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Original Research Paper

Paediatrics

COMPARATIVE EVALUATION OF GROWTH PARAMETERS OF IVF(TEST-TUBE-BABY) CHILDREN AND NON IVF CHILDREN

Dr Randhir Singh Assistant Professor Dept. Of Paediatrics, L.N Medical College & J.K. Hospital, Bhopal, MP

Dr Monica Singh* Assistant Professor Dept. Of Obstetrics & Gynaecology, L.N Medical College & J.K. Hospital, Bhopal, MP *Corresponding Author

ABSTRACT

Background: Fertility rates have started declining in MP, India in the last few decades. In vitro fertilization (IVF) is one of the major treatment modalities available to infertile couple.

Aims This study was aimed to evaluate and compare the growth parameters of IVF and spontaneously conceived children. The objective of this study was to relate the physical growth status of IVF children with that of spontaneously conceived group.

Material and Methods Weight and height of up to 14-year-old children were assessed. Birth weight and length of each case and control group was also recorded. The case group consisted of term, singleton babies who were outcome of IVF in the studied area . The control group consisted of term, first child, singleton, and spontaneously conceived up to 14-year-old children who were also resident of the studied area. A sample of 200 IVF and 200 NON-IVF ,spontaneously conceived children were examined. Statistical Analysis Used: Chi-square and student's t-test were used for data analysis.

Results: In a cross-sectional case-control study, growth parameters of up to 14-year-old children were assessed.No statistically significant difference found in the studied (IVF children) and the control group (NON-IVF, spontaneously conceived children).

Conclusion: No statistically significant difference was observed in growth parameters between IVF and NON-IVF,spontaneously conceived children

KEYWORDS : Child Development ,Growth ,IVF, Morbidity

INTRODUCTION

The first test tube baby in the world, Louise Brown,[1] was born on 25 July 1978 after in vitro-fertilization (IVF) by R. G. Edwards and P. Steptoe in Oldham, (1978)[1]England. This laid the foundation of Assisted Reproductive Technologies (ART) and was a landmark in infertility treatment.

India was not far behind in the scientific and technological developments of test tube baby procedure. A few days after the delivery of the first test tube baby in UK, an Indian team from Kolkata led by (Late) Dr. Subhas Mukherjee,[2] an excellent cryobiologist, and (Late) Dr. Saroj Bhattacharya,[2] a well-known gynecologist, announced the birth of "Durga",[2] following a test tube baby procedure, on 3 October 1978. Dr. Mukherjee's work was initially not accepted because of lack of adequate scientific documentation. However, subsequently (2003) his work was recognized as authentic by Indian Council of Medical Research (ICMR) and his team has been accredited for delivering the first test tube baby in India and the second one in the world. After that, Dr. T. C. AnandKumar[2] first scientifically documented test tube baby in India on 6 August 1986 in Mumbai.

Olivennes et al., (2002)[3] found prematurity, low birth weight, and perinatal mortality were higher in children born after IVF than in the general population. Pinborg et al., (2003)[4] observed no major differences in physical health between IVF/intracytoplasmic sperm injection (ICSI) twins and non-IVF/ICSI twins. Koivurova et al., (2003)[5] compared the main developmental milestones in children born after IVF with spontaneously conceived matched controls. They hypothesized that IVF children reach developmental milestones later. They observed that the growth of IVF children was behind that of control children during the first 3 years of life, but their psychomotor development was similar.

The present study was carried out with an aim to correlate the physical status of IVF children with that of spontaneously conceived children. Our specific objective was to determine the growth pattern of IVF children and how it differs from NON-IVF children.

MATERIALS AND METHODS

Study design/Type of study - This is a descriptive, analytic, cross-sectional study approved by the LN MEDICAL COLLEGE & JK HOSPITAL- Research Ethical Committee.

Sample size & Duration of study- Total 800 parents of the studied samples were approached to participate in the present study (400 IVF parents and 400 parents of spontaneously conceived children). Out of the above total, 200 IVF and 200 NON-IVF, normal spontaneously conceived children's guardian agreed to participate in the present study. Growth parameters (height and weight) of up to 14-year-old children were evaluated at one point of time from - JAN 2016 to DEC 2018 in both Obstetrics - Gynaecologyand Pediatric department of LN MEDICAL COLLEGE, BHOPAL.

Inclution & Exclution criteria: The children in both case and control groups based on the route of pregnancy were enrolled for the entire course of study. In the IVF children group, gestational age were 32 to 42 weeks, singleton babies who were outcome of IVF , were chosen by a computer-generated random number list. The control group consisted of term , singleton, and spontaneously conceived up to 14-year-old children whom were referred to Department of paediatrics for health cheek-up from department of Obstetrics- Gynaecology. Case and control matched for year of birth, area of residence, parity, gestational age, maternal weight, maternal age, and socioeconomic status. Medical records of both groups were reviewed and variables such as sex, gestational age, birth weight and length, route of delivery, maternal age, and parity were recorded. Multiple pregnancies, severe asphyxia, children with major congenital malformations, chromosomal abnormalities, and genetic syndromes were excluded in the present study.

Data collection procedure : Case and control matched for year of birth, area of residence, parity, gestational age, maternal weight, maternal age, and socioeconomic status. Medical records of both groups were reviewed and variables such as sex, gestational age, birth weight and length, route of

delivery, maternal age, and parity were recorded. The weights of all samples were taken with a children's weighing scale with sensitivity of 10 g. The weighing scale was calibrated at regular intervals. The standing crown heel height was measured using a stadiometer. To eliminate error due to inter observer variations, all measurements were made by a trained single examiner of research who was not informed about the birth status of the children. The study was conducted after informed consent was obtained from the concerned authorities and the guardians of the children. The subjects without shoes and in light summer dress were asked to stand on a weighing machine.

The weight was recorded in kilograms. It was important that child should stand in the middle of the weighing machine. The weighing scale should be corrected for any zero error before measurement. The children were taken to the vertical scale i.e. stadiometer, graduated in centimeter, for measuring height. They were asked to take off their shoes and stand with both feet together. The subjects were then positioned in such a manner that their heels, buttocks, scapulae, and occiput should be touching the vertical support of the stadiometer and head should be straight without any bending.

Head was so positioned that the child looked directly forward with the Frankfurt plane (the line joining the floor of external auditory meatus to the inferior margin of orbit), and the biauricular plane should be horizontal. The horizontal headboard was then brought down and kept firmly over the vertex end to compress the hair and touch the maximum height of the scalp. The measurement of height was then recorded in centimeter. During history taking, birth weight and length of case and control group was also recorded.

OBSERVATIONS

TABLE 1: SEX WISE DISTRIBUTION OF IVF CHILDREN AND SPONTANEOUSLY CONCEIVED CHILDREN

Type of delivery	Male (%)	Female (%)	Total (%)
IVF Children	100 (50)	100 (50)	200(100)
NON-IVF (Spontaneously conceived children)	100(50)	100(50)	200(100)
Total	200(50)	200 (50)	400(100)

IVF: In vitro fertilization

TABLE 2: PERCENTAGE DISTRIBUTION OF IVF AND NON-IVF, SPONTANEOUSLY CONCEIVED CHILDREN IN RELATION TO PRESENT HEIGHT AND WEIGHT

	IVF Children		Non-IVF Children	
Age	Height (Kg)	Weight (Kg)	Height (Kg)	Weight (Kg)
Birth	48.63	2.61	48.91	2.93
1	71.74	7.96	72.61	8.82
2	83.81	10.97	84.72	11.06
3	80.12	12.52	89.01	13.49
4	89.71	15.97	102.33	16.02
5	102.95	17.55	112.45	19.16
6	110.62	20.08	120.43	23.62
7	125.14	25.36	127.78	24.36
8	127.61	28.42	130.38	32.47
9	131.2	29.5	132.4	33.72
10	133.87	31.42	134.25	34.62
11	138.11	36.41	142.57	35.72
12	145.1	44.72	146.1	45.05
13	153.5	47.5	159.5	55
14	164.3	50.70	165.77	58.79

Table 3: Mean weight birth in IVF and spontaneously conceived children

Weight birth (KG)		
IVF	2.6	t=5.14
Normal	2.9	P<0.001

IVF: Invitro fertilization

TABLE4: MEAN LENGTH AT BIRTH IN IVF AND SPONTANEOUSLY CONCEIVED CHILDREN

Length birth (cm)		
IVF	48.6	t=1.62
Normal	48.9	P<0.05

IVF: *Invitro fertilization*

TABLE5: STATISTICAL ANALYSIS OF PRESENT HE IGHT OF IVF AND SPONTANEOUSLY CONCEIVED CHILDREN

HEIGHT	*X*	SD	*'T'*
IVF	12625.27		*'t'*0.53
NON-IVF, children	13122.23	d.f=22	*P*>0.05

SD:Standarddeviation, IVF:*Invitro*fertilization

TABLE6:STATISTICAL ANALYSIS OF PRESENT WEIGHT OF IVF AND SPONTANEOUSLY CONCEIVED CHILDREN

WEIGHT	*X*	SD	*'T'*
IVF	3030.08	0.009	
NON-IVF,	31	31.88	d.f=22*P*>0.05

SD:Standarddeviation, IVF:*Invitro*fertilization

RESULTS

A total of 200 IVF children and 200 spontaneously conceived children were studied. Among 200 IVF children, 100 (50%) were male and 100 (50%) were female. Among spontaneously conceived children, 100 (50%) were male and 100(50%) were female. Distribution of the sample based on age and sex are depicted in Table 1 and Percentage distribution of height and weight of IVF children and naturally conceived children are described in Table 2.

The mean birth weight of the IVF children was found to be 2.6 kg and the mean birth weight of the spontaneously conceived children was 2.9 kg, t value was 5.14, d.f = 298, P < 0.001 and the result was statistically significant. The mean birth length of IVF children was found to be 48.6 cm and the mean birth length of the spontaneously conceived children was 48.9 cm, t value was 1.63, d.f = 298, P > 0.05 and the result was statistically nonsignificant [Tables 3-4].

The mean height of the IVF children was found to be 126 cm (SD 25.275) and the mean height of the spontaneously conceived children was 131 cm (SD 22.23), t value was 0.51, d.f = 22, P > 0.05 and the result was statistically nonsignificant. The mean weight of the IVF children was found to be 30 kg (SD 30.08) and the mean height of the spontaneously conceived children was 31(SD 31.88), t value was 0.009, d.f = 22, P > 0.05 and the result was statistically nonsignificant [Tables 5 and 6]. The differences in averages of height and weight between the IVF and spontaneously conceived children are both statistically nonsignificant as found by student's t test

STATISTICAL ANALYSIS

After getting the required information, the collected data were coded, tabulated and analysed. The various statistical techniques i.e. the mean, standard deviation and test of significance (t-test and chi-square-test) were used for drawing valid conclusions.Statistical analysis done using student t-test. SPSS 13.0 software was used to calculate p value.P<0.05 was taken as statistically A descriptive analysis was done on all variables to obtain a frequency distribution. The mean + SD and ranges were calculated for quantitative variables. Continuous variables were compared by the Student t test. Proportions were analyzed with the chi-square test

DISCUSSION

The child is not just a miniature adult but a dynamic organism undergoing constant physical changes. The new WHO Child Growth Standards reveal that children born anywhere in the world and given the optimum start in life have the potential to develop to within the same range of height and weight. Although there are individual differences among children, but within large populations, regionally and globally, the average growth is similar.

Children from India, or any other country way reflect similar growth patterns when provided healthy growth conditions in early life. The new standards prove that differences in children's growth up to the age of 14 years are more influenced by nutrition, feeding practices, environment, and health care than genetics or ethnicity.

Olivennes F, Fanchin R et al did work on perinatal outcome and developmental studies on children born after IVF . A high rate of adverse outcome has been demonstrated in a large group of IVF pregnancies. Prematurity, low birth weight and perinatal mortality are higher than in the general population. The majority of these complications are related to multiple births, but they are also found in singleton pregnancies. An analysis of the multiple risk factors involved in these complications was needed. The infertile status of IVF patients clearly plays a role in the risk of adverse outcome. Age and parity may be important factors. The role of IVF itself has not been demonstrated convincingly. The effect of ovarian stimulation deserves further study. Most of the studies published on the follow-up of IVF children are reassuring, but it is clear that these studies are not sufficient to eliminate without doubt any adverse effects on the well-being of IVF children. All IVF pregnancies should be followed with great care, not because they are more precious than spontaneous pregnancies, but because they are exposed to an increased risk of complications. The main problem of IVF remains the high rate of multiple pregnancies, including twins.[3]

Pinborg A et al studied morbidity in a Danish national cohort of 472 IVF/ICSI twins, 1132 non-IVF/ICSI twins and 634 IVF/ICSI singletons: health-related and social implications for the children and their families. No major differences in physical health were observed between IVF/ICSI twins and non-IVF/ICSI twins. Nevertheless, the only predictor of low divorce/separation risk was IVF/ICSI treatment. To conclude , Our study indicates that physical health of IVF/ICSI twins is comparable with that of non-IVF/ICSI twins. However, physical health of IVF/ICSI twins is poorer and the implications for the families stronger compared with IVF/ICSI singletons.[4]

Koivurova S et al did work on growth, psychomotor development and morbidity up to 3 years of age in children born after IVF. The authors conducted a population-based cohort study. Infant mortality in the IVF group was >2-fold higher compared to the national rate in the general population. No statistically significant differences were found in the psychomotor development between the cohorts. Cumulative incidence of different diseases up to 3 years of age was significantly higher among IVF children in the full sample and singleton analyses The growth of IVF children was behind that of control children during the first 3 years of life, but their psychomotor development was similar. Their postnatal health was worse, probably reflecting the problems in the neonatal period.[5]

First study on physical status evaluation was done by De Monte Beillard (1759-1776).[6] First study of growth was published by Scamman in 1927.[6] After that, various studies were done by different national and international scientists.In India, first study was conducted by Ghosh, Sen, and Chandrasekhar in 1944.[6] From their study, they came to the conclusion that physical status may vary from person to person, race to race, state to state, or country to country. This inspired the present study to determine the physical status of IVF children.In our present study, it was found that both height and weight of IVF children were increasing steadily like spontaneously conceived children. When regression equation had been worked out between height and weight for both IVF and spontaneously conceived children, the regression equations expressed the linear relationship between height and weight of children in two groups (IVF and NON-IVF, spontaneously conceived children). It denotes that the physical growth of IVF children were proportionate with that of normal children.[6]

Wennerholm UB et al studied postnatal growth and health in children born after cryopreservation as embryos. The authors investigated the postnatal growth and health (up to 18 months) of these children compared with those born after standard IVF with fresh embryos and those from spontaneous pregnancies.Growth features were similar for both singletons and twins in the three groups. There were 6 (2-4%) of 255, 9 (3-5%) of 255, and 8 (3-2%) of 252 major malformations in the cryopreserved group, standard IVF, and spontaneous groups, respectively (p=0-6 between the cryopreserved and standard IVF group). The cryopreservation process does not adversely affect the growth and health of children during infancy and early childhood. Minor handicaps, behavioural disturbances, learning difficulties, and dysfunction of attention and perception cannot be ruled out at this age.[7]

Bergh T, Ericson A et al did a retrospective cohort study of deliveries and children born after in-vitro fertilisation in Sweden 1982–95 .In-vitro fertilisation is an effective treatment for infertility, but there is concern about the health of children. Data were stratified for maternal age, parity, previous subfertility, year of birth, and multiple of pregnancies.A high frequency of multiple births and maternal characteristics were the main factors that led to adverse outcomes, and not the in-vitro-fertilisation technique itself. The clinical practice of in-vitro-fertilisation needs to be changed to lower the rate of multiple pregnancy.[8]

Gissler M et al studied in-vitro fertilization pregnancies and perinatal health .The purpose of this study was to compare IVF mothers with other mothers, and the perinatal health and health care costs of IVF infants to those of other infants. They started antenatal care earlier, had more visits than other mothers and more than 50% were hospitalized during their pregnancy. Every fourth IVF pregnancy was a multiple one. Both IVF singletons and multiples had poorer health than other infants. The health care costs for one IVF newborn from induction of pregnancy until the age of 7 days was 5.4-fold compared to other newborns. The subsequent health of IVF children has to be further studied to more fully assess the health impact of IVF.[9]

Ceelen M et al studied growth during infancy and early childhood in relation to blood pressure and body fat measures at age 8–18 years of IVF children and spontaneously conceived controls born to subfertile parents. The follow-up study comprised 233 IVF children aged 8–18 years and 233 spontaneously conceived controls born to subfertile parents. Growth data from birth to 4 years of age, available for 392 children (n = 193 IVF, n = 199 control), were used to study early post-natal growth. We found significantly lower weight, height and BMI standard deviation scores (SDSs) at 3 months, and weight SDS at 6 months of age in IVF children compared with controls .Late infancy growth velocity of IVF children was significantly higher compared with controls. Nevertheless, early childhood growth instead of infancy growth seemed to predict cardiovascular risk factors in IVF children. Further

research is needed to confirm these findings and to follow-up growth and development of IVF children into adulthood.[10]

Yovich JL et al studied developmental assessment of twenty in vitro fertilization (IVF) infants at their first birthdayAn increased rate of preterm delivery. intrauterine growth retardation, and cesarean sections was noted. One significant and two minor abnormalities were detected and only one infant was slightly under the expected developmental assessment at 1 year on the corrected general quotient of the Griffiths Developmental Scales for children.[11]

In a study similar to our study ,Morin NC, Wirth FH et al did their study on congenital malformations and psychosocial development in children conceived by in vitro fertilization. To determine whether in vitro fertilization (IVF) as a method of conception is associated with an increased risk for congenital malformations or developmental dysfunction, the authors performed a general physical examination for malformations, neurologic examination, developmental examination (Bayley Scales), echocardiography, electrocardiography, abdominal ultrasound study, and, when possible, cranial ultrasound examination on a cohort of 83 IVF children and 93 matched non-IVF children. Based on these small numbers but extensive evaluation, we found no association between conception by IVF and an increased risk for congenital malformations. Likewise, children conceived by IVF showed no evidence of developmental delay. Their high average achievement on the Bayley tests probably resulted from the exceptional motivation of their parents ("wantedness") and their generally high socioeconomic status.Theresults of their study also corroborated with our study.[12]

Castillo CM et al studied the impact of IVF on birthweight from 1991 to 2015: a cross-sectional study. IVF conceived singletons have had a higher incidence of low BW compared to spontaneously conceived singletons, and this has raised concerns over long-term increased risks of cardio-metabolic disease. However, few causal links between IVF procedures and BW have been robustly established, and few studies have examined whether BW has changed over time as IVF techniques have developed. Multiple linear regression analysis was used to evaluate associations between IVF treatment parameters and BW, after adjusting for the year of treatment and patient characteristics and pregnancy factors.There has been a progressive BW increase in IVF singletons over time in one large centre with consistent treatment eligibility criteria. Such a change is not seen in the general population of live born singletons in the UK or other developed countries, and seems to be specific to this IVF population. This may be a reflection of changes in practice such as undisturbed extended embryo culture to the blastocyst stage, optimized commercial culture media composition, single embryo transfer and ICSI. Moreover, singletons conceived from frozen/thawed embryos had higher birth weights when compared to their fresh embryo transfer counterparts. [13]

The causal pathway is unknown; however, it could be due to the impact on embryos of the freeze/thaw process, self-selection of embryos from couples who produce a surplus of embryos, and/or embryo replacement into a more receptive maternal environment.IVF conceived singletons have had a higher incidence of low BW compared to spontaneously conceived singletons, and this has raised concerns over long-term increased risks of cardio-metabolic disease. However, few causal links between IVF procedures and BW have been robustly established, and few studies have examined whether BW has changed over time as IVF techniques have developed.(13), and also no association between IVF and NON-IVF Children regarding any difference in both groups.(14)

Our study supports the findings of earlier studies.Olivennes et al.,[3] and Wennerholm et al.[7].Also we observed that the studied IVF children had relatively low birth weight than the NON-IVF, spontaneously conceived children. This finding supports the previous studies done by Olivennes et al.,[3] Bergh et al.,[8] Gissler et al.,[9] and Koivurova et al.[5]. Length at birth was also found to be lower in IVF children then spontaneously conceived children but the result was not statistically significant ($P > 0.05$). Ceelen et al.[10] found low infancy growth velocity was significantly higher in IVF children and did not matched with the present study. Youich et al.,[11] Morin et al.,[12] Wennerholm et al.,[7] Pindborg et al.,[4] also found no difference in IVF children when compared with NON-IVF, spontaneously conceived ones. [14]

CONCLUSION

In our study, no statistically significant difference was observed between IVF and spontaneously conceived children. Growth assessment and a timely and regular follow-up is necessary for early detection of any growth disorders of IVF children. More studies are required to evaluate the relationship among the growth and development of IVF and NON-IVF children. The present study tried to find out through the obtained data whether the IVF children were at par with the NON-IVF ,spontaneously conceived children in their physical aspects or not. This study is also significant from ethical and social perspective as it motivates the parents of IVF children in a positive manner. On the basis of that information, a specific useful growth chart can be formulated to initiate further studies in this new medical field.

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Ethical approval : Taken

WHAT THIS STUDY ADD TO EXISTING KNOWLEDGE : Thus, we derived from our study that the IVF group of children were no longer inferior to the NON-IVF, spontaneously conceived group during physical status evaluation soon after birth. There are scopes for longitudinal study with more parameters. Future more studies are required which may accumulate more information about IVF children.

LIMITATION OF OUR STUDY

1. The independent variables included in the study were limited to those that have been consistently recorded and stored electronically over the past two decades.
2. Chances of bias
3. Single center trial

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